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Efficient Preparation of Trisubstituted Alkenes Using the Julia-Lythgoe Olefination of Ketones. On the Key-Role of SmI_2 in the Reductive Elimination Step.[¥]

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[¥] Dedicated with deep respect to Professor Marc Julia

Abstract: Modification of the Julia-Lythgoe olefination reaction between ketones and primary sulfones leads to trisubstituted alkenes in good overall yields. Samarium diiodide is shown to play a crucial role in the reductive elimination step.

During the course of a total synthesis, we required the preparation of trisubstituted alkenes **3** from methyl ketones **1** and decided to use the Julia-Lythgoe olefination reaction (Figure 1).[1]

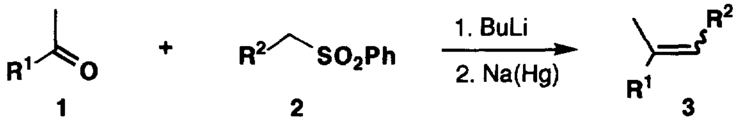


Figure 1

Examination of the literature revealed that the vast majority of reports on the preparation of trisubstituted olefins using the Julia-Lythgoe protocol employ, as the first step, the condensation between a disubstituted sulfone anion **4** and an aldehyde **5**, rather than the alternative process, the addition of a monosubstituted sulfone anion **9** to a ketone **10** (Figure 2).[2]

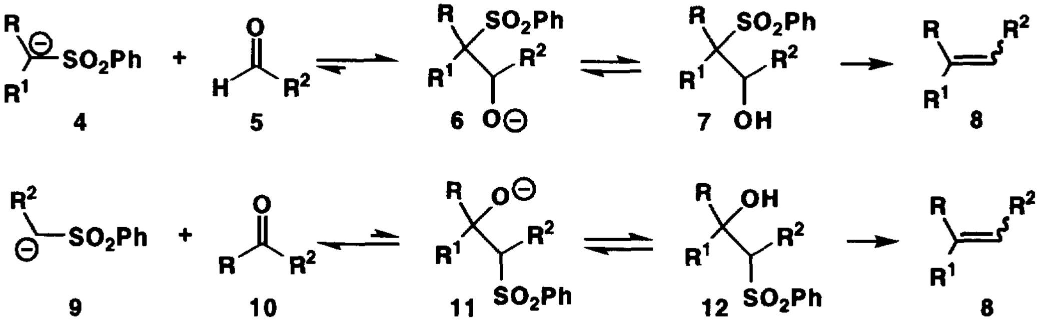
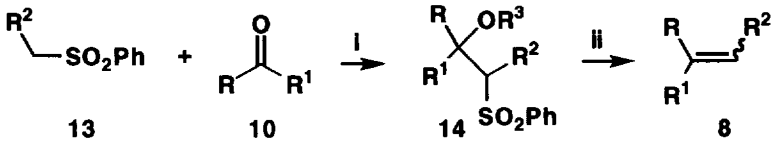


Figure 2

Two reasons are held responsible for the poor yields of the olefination represented in Figure 1. Firstly, whereas the anion **4** adds to aldehyde **5**, generating in high yield the β-hydroxysulfone **7**, the corresponding reaction between sulfone anion **9** and ketone **10** is a reversible process with the equilibrium lying mostly towards the starting materials. Usually, poor yields of β-hydroxysulfone **12** are obtained *via* this route. Secondly, during the Na(Hg) mediated reductive elimination, deprotonation of **12** takes place competitively with alkene formation, even under buffered conditions leading, besides the desired olefin **8**, to substantial quantities of starting material, originating from the fragmentation of alkoxide **11**.[3] Therefore, we initiated some model studies with the hope of improving the Julia-Lythgoe olefination of ketones.

At the onset, it was realised that improved yields of β-hydroxysulfones **12** might be obtained by selective *in situ* quenching of the incipient alkoxide **11**. Thus, sulfones **13** were deprotonated using nBuLi and the resulting anions reacted with ketones **10**. Trapping of the tertiary alkoxide adducts with either Me_3SiCl or PhCOCl, followed by aqueous work-up, lead in high yield to the β-hydroxysulfones **14** (R_3=H) and the β-sulfoxy-benzoates **14** (R_3=COPh). Some representative examples of this condensation are collected in Table 1.

Table 1. Modified Julia-Lythgoe Olefination Reaction



Entry	R^2	R	R^1	R^3	14 (%)	8 (%)
1	nC_6H_{13}	$PhCH_2CH_2$	CH_3	H	69	66[a]
2	nC_6H_{13}	$PhCH_2CH_2$	CH_3	PhCO	81	72[b,c]
3	CH_3	nC_4H_9	CH_3	H	86	69[a]
4	CH_3	nC_4H_9	CH_3	PhCO	93	73[b]
5	nC_6H_{13}	H	$PhCH_2CH_2$	PhCO	88	64[b]
6	CH_3	CH_3	$PhCH_2CH_2$	PhCO	82	84[b]

i = nBuLi, THF, -78°C to 20°C then Me_3SiCl or PhCOCl, -78°C to 20°C; ii = SmI_2, THF, HMPA. (a) = Reaction performed at 0°C; (b) = Reaction performed at -78°C; (c) = An 84% yield of alkene was obtained when the reductive elimination was performed at -85°C; All yields are for pure, fully characterised, products. Olefin ratios are typically in the range 2:1 (*E/Z*).

With expedient access to the desired adducts, attention was then directed towards the reductive elimination step. The use of Na(Hg) amalgam, whether buffered or not, quickly proved to be unsuitable to our purpose, resulting either in poor yields of alkene or in complete decomposition of the starting material. Amongst several other reducing agents, the lanthanides appeared particularly attractive and SmI_2 was tested in this transformation.[4]

However, in stark contrast to Na(Hg) amalgam, SmI_2 in THF does not effect the reductive elimination of β-hydroxyphenylsulfones, even after prolonged reaction times at room temperature.[5] This lack of reactivity was noticed earlier by Kende who utilised *N*-methylimidazolylsulfone, a better single-electron acceptor, as a substitute for the more classical, but inert, phenylsulfone.[6] While the use of this group offers an ingenious solution, we decided to test the influence of certain additives,[7] known to significantly alter the reducing ability of SmI_2, in the reductive elimination of phenylsulfones. Much to our delight, using the Inanaga conditions (1-5 mol% HMPA in THF),[8] substrates **14** underwent smooth transformation into an *(E)/(Z)* mixture of alkenes **8** in good to excellent yields (Table 1).[9] Recently, Fukumoto[10] and Keck,[3] independently reported a similar use of the SmI_2/HMPA system in the preparation of disubstituted olefins.

The reductive elimination of β-hydroxysulfones **15** and β-sulfoxybenzoates **19** also displays intriguing features.[9] Perhaps the most noteworthy is the enormous difference in rate in the formation of the alkene **8** from alcohol **15** and its benzoyl analogue **19** (Figure 3). Whereas the benzoate derivative **19** affords the required olefin **8** at temperatures as low as -85°C within a few minutes, the hydroxy sulfone **15** is recovered unchanged under similar conditions.

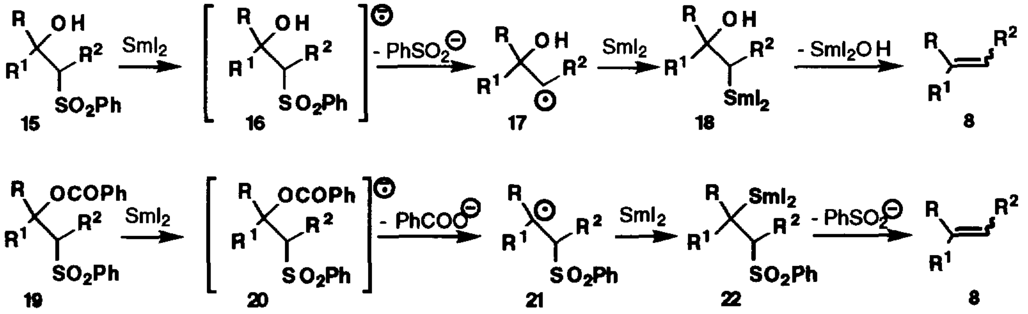


Figure 3

These observations strongly suggest that the SmI_2 mediated reductive elimination of **15** and **19** proceeds by different mechanisms. We believe that in the case of the β-hydroxysulfone **15**, a single electron transfer from the SmI_2 to the aromatic sulfone moiety generates the radical anion **16**. This rather difficult step is then followed by the expulsion of phenylsulfinic anion, leading to radical **17**. A second electron transfer from SmI_2 results in the organosamarium compound **18** which eliminates SmI_2OH. In contrast, transfer of an electron from SmI_2 to the benzoate function is a much easier process[11] resulting, through the intermediacy of radical anion **20**, radical **21** and organosamarium derivative **22**, in the formation of **8** (Figure 3).

This difference in rate of reductive elimination can also be exploited in further synthetic transformations. For example, upon treatment with SmI_2 in THF containing 4% of HMPA, the mono-benzoylated *bis*-sulfone **23** undergoes smooth and chemoselective elimination of the β-sulfoxybenzoate fragment, giving in good yield the unsaturated hydroxysulfone **24** (Figure 4).

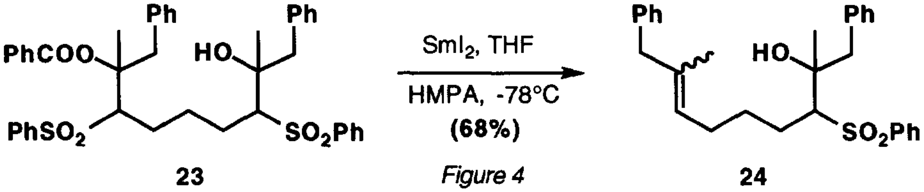


Figure 4

In summary, we have shown that modifications of the Julia-Lythgoe olefination protocol, using SmI_2/HMPA as a key-reducing agent,[12] can lead to the efficient preparation of trisubstituted alkenes from ketones. The differential in reactivity between β-hydroxysulfones and β-sulfoxybenzoates can be utilised for the chemo- and regio-selective generation of a carbon-carbon double bond in polyfunctional substrates. Further work aimed at delineating the scope of this reaction and applying it to the synthesis of complex natural products is currently underway in our laboratory. The results of these studies will be reported in due course.

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